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Proteolytic cleavage, trafficking, and functions of nuclear receptor tyrosine kinases

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Abstract

Over three quarters of receptor tyrosine kinase (RTK) families are reported to have intracellular localization in response to environmental stimuli. Internalized RTK can bind to non-canonical substrates and affect various cellular processes. Many of the intracellular RTKs exist as fragmented forms that are generated by γ-secretase cleavage of the full-length receptor, shedding, alternative splicing, or alternative translation initiation. Soluble RTK fragments are stabilized and intracellularly transported into subcellular compartments, such as the nucleus, by binding to chaperon or transcription factors while membrane-bound RTKs (full-length or truncated) are transported from the plasma membrane to the endoplasmic reticulum (ER) through the well-established Rab- or clathrin adaptor protein (AP)-coated vesicle retrograde trafficking pathway. Subsequent nuclear transport of membrane-bound RTK can occur via two pathways, INFS and INTERNET, with the former characterized by the release of receptors from ER into the cytosol and the latter by the release of membrane-bound transport from the ER into the nucleoplasm through the inner nuclear membrane. While most non-canonical intracellular RTK signaling is related to transcriptional regulation, there may be other functions that have yet to be discovered. In this review, we summarize the proteolytic processing, intracellular trafficking, and nuclear functions of RTKs and discuss how they promote cancer progression and their clinical implications.

Graphical Abstract

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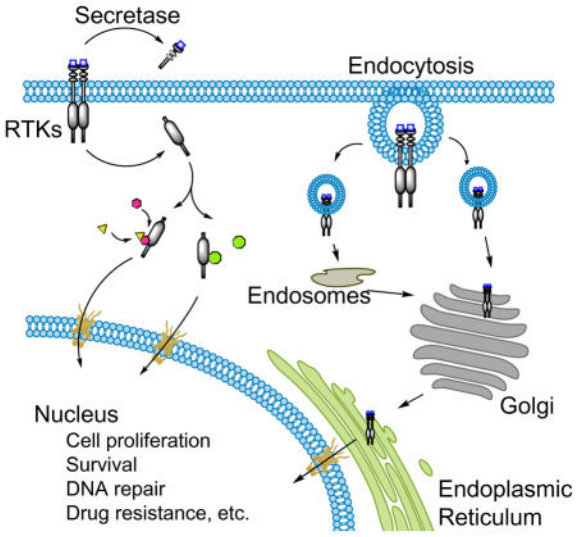

Keywords

Receptor tyrosine kinase; proteolytic cleavage; nuclear translocation; intracellular trafficking

1. Introduction

Receptor protein kinases play critical roles in the regulation of normal biological processes in response to stimuli. However, dysregulation of these kinases, especially when their substrates are also kinases, can further amplify aberrant signaling that leads to diseases such as cancers. Among the receptor protein kinases, receptor tyrosine kinases (RTKs) are thought to be the largest catalytic membrane receptor family, and the development and progression of many human diseases have been attributed to the dysregulation of these RTKs. There are a number of well-characterized and FDA-approved targeted cancer therapies against RTKs, including monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs) [1].

The protein structures, mechanisms of activation, and downstream regulatory pathways of RTKs are highly conserved from *C. elegans* to humans [2]. In humans, there are 58 known RTKs classified into 20 subfamilies [3]. A prototypical RTK consists of an extracellular ligand-binding domain, a single transmembrane helix domain, a juxtamembrane regulator domain, a cytoplasmic domain containing the tyrosine kinase (TK) domain, and a carboxyl terminal (C-term) domain (Figure 1). Discovered as cell surface proteins, RTKs are membrane receptors that have high affinity for extracellular growth factors, cytokines, and hormones [4]. Overexpression and mutation of RTKs as well as dysregulation of their signaling lead to human diseases, including cancer [5]. While therapeutics against RTKs and their downstream molecules have demonstrated effectiveness in treating cancer, acquired drug resistance and toxicity have also been observed [6, 7]. Thus, investigations are currently underway to further our understanding of RTK signaling toward the development of more effective drugs.

In the past, a majority of studies have focused on canonical RTK signaling from the cell surface via the following sequential events (Figure 2): (1) The receptor binds with its ligand and then (2) undergoes conformational changes and forms homo- or hetero-oligomers that are essential to activate its kinase activity. The tyrosine kinase domain then undergoes *trans* autophosphorylation that greatly elevates the receptor's catalytic activity. (3) The phosphotyrosine residues serve as docking site for cytoplasmic adaptor proteins containing Src homology-2 (SH2) and phosphotyrosine-binding (PTB) domain to form signal transduction complex that determines and initiates the corresponding signaling cascade to regulate cellular processes in response to ligand stimulation [3, 8–13].

Interestingly, members of the RTK subfamilies are also present in the nucleus and are referred to as **m**embrane **r**eceptor **i**n **n**ucleus or MRIN [14, 15]. Accumulating evidence indicates at least 12 RTK families contain MRINs that exist either as holoreceptor or truncated form with novel non-canonical functions in transcriptional regulation, DNA damage and repair, and cell proliferation and invasion [15–19]. In various cancer types, nuclear RTK expression is associated with poor prognosis [20–23]. Generally, after ligand-induced activation, membrane-bound MRINs are internalized through endocytosis from the cell surface and then transported into the nucleus. Moreover, RTKs can be proteolytically cleaved to release an active RTK fragment that is also transported from the cell membrane to subcellular compartments, including the nucleus.

Drugs that target aberrantly expressed RTKs are designed base on the canonical RTK functions, but they can also lead to drug resistance by inducing RKT internalization. For example, EGFR inhibitors, gefitinib and cetuximab, have both been reported to enhance the levels of nuclear EGFR (nEGFR), which in turn lead to the development of resistance [24–27]. Huang et al. observed increased EGFR in the nucleus of gefitinib-resistant cancer cells and found that nEGFR promotes the transcription of the multidrug resistance efflux transporter breast cancer-resistance protein (BCRP/ABCG2) [25]. Thus, identifying the mechanisms underlying RTK translocation may enhance our understanding of drug resistance. In this chapter, we summarize the proteolytic cleavage processing, mechanisms of nuclear transport, and non-canonical function of RTKs. We mainly focus on members of the ErbB family while briefly discussing other MRINs.

2. Generation of intracellular RTK fragments

Intracellular RTKs do not always exist in the holoreceptor form. Rather, they can be proteolytically cleaved to release an active RTK fragment that is also transported from the cell membrane to subcellular compartments. Cleavage at the transmembrane domain of RTK, which yields an intracellular domain (ICD), can occur by different mechanisms in response to various stimuli [14]. These include caspase-, splicing- and secretase-dependent pathways. Among them, RTK fragments generated by secretase-mediated and splicing are reported to have nuclear localization and functions.

2.1 Caspase-dependent RTK fragment

Many RTKs, including Ret, c-MET, tropomyosin receptor kinase (Trk)-C, anaplastic lymphoma kinase (ALK), ErbB-1/epidermal growth factor receptor (EGFR), ErbB-2/

HER-2, and Eph-A4, are subjected to caspase cleavage. Except for EGFR, most of the caspase-dependent intracellular fragments have a direct role in determining the cell fate (reviewed in [28]). Most caspase-mediated RTK cleavage generates detectable fragments that lack the extracellular domain as well as the C-terminal docking sites for downstream signaling proteins. Examples of the caspase-cleaved RTK fragments include intact TK domain of Ret and MET, truncated TK domain of Trk-C, ALK and Eph-A4, and truncated C-term domain of EGFR and ErbB-2. Of these, Ret, MET, Trk-C, and ErbB-2 fragments are also pro-apoptotic factors as they can promote apoptosis without ligand activation [28]. RTK phosphorylation has been shown to inhibit caspase-dependent cleavage [29], suggesting that RTK-addicted cells may rely on not only ligand-stimulated canonical signaling but also inhibition of caspase-related pro-apoptotic factors.

2.2 Alternative splicing RTK variants

Aside from caspase-mediated cleavage, truncated RTKs can also be generated from alternative mRNA splicing. Alternative pre-mRNA splicing is a process that generates mRNA variants of the same gene, yielding structurally and functionally different proteins. Many of the RTK splice variants have distinct functions from the holoreceptor and are also implicated in cancer development [30]. Below we briefly describe some examples of alternative splicing-generated RTK variants.

Both EGFR and ErbB-3 of the ErbB family are known to have alternative splice variants. There are four EGFR splice variants, EGFRvI, II, III, IV, and an in-frame splice variant known as mini-LEEK (mLEEK). Among them, EGFRvIII and mLEEK are known to localize to the nucleus to regulate cellular responses. EGFRvIII is produced by deletion of exons 2–7 of the *EGFR* gene [31] while mLEEK lacks exons 1 to 23 [32]. Another well-known alternative spliced RTK is TrkA. There are several *TrkA* splice variants found in neuroblastoma, including TrkAI and TrkAII from exon 9 alternative splicing [33], and TrkAIII from deletion of exons 6, 7, and 9, and extracellular IG-C1 and N-glycosylation domains [34]. Both TrkAI and TrkAIII are reported to affect tumor progression in neuroblastoma cells with TrkAI acting as a tumor suppressor and TrkAIII as an oncogene [35]. In the presence of Hsp90 inhibitor geldanamycin, cytosolic TrkAIII binds to Hsp90, which has been shown to render neuroblastoma cells resistant to geldanamycin–induced apoptosis [35]. TrkAIII also has been reported to localize to the centrosome where it causes genetic instability [35].

2.3 Protease-dependent RTK cleavage

Generally, upon ligand binding, RTKs can undergo multiple proteolytic cleavages in a protease-dependent manner (reviewed in [36]). For example, members of at least 10 RTK subfamilies undergo a series of secretase cleavage after activation to remove the extracellular domain followed by the release of the intracellular domain from the cell membrane, a process that is also known as regulated intramembrane proteolysis (RIP) [37]. α-secretases, e.g., matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase (ADAM), and β-secretases, e.g., aspartic proteases (BACE), are responsible for RTK ectodomain shedding, which releases the extracellular domain of surface membrane RTK by proteolytic cleavage adjacent to the plasma membrane [38].

Among these proteases, ADAM-10 and ADAM-17/TACE (tumor necrosis factor-α-converting enzyme) are responsible for the majority of RTK shedding that generates a soluble ectodomain and a membrane-anchored carboxyl-terminal fragment (CTF) [39]. ADAM possesses higher substrate specificity than MMPs and cleaves substrates containing Ala-Val [40–42]. By using a peptide library, Caescu *et al*. demonstrated that ADAM17 specifically selects for small aliphatic residues immediately downstream of the cleavage site while ADAM10 can tolerate aromatic residues at that position [43]. After shedding, the intramembrane protease complex γ-secretase is responsible for the recognition and intramembrane cleavage of transmembrane proteins to release intracellular protein fragments (reviewed in [44]). The multi-subunit γ-secretase complex contains an enzymatic core comprised of presenilin, presenilin enhancer-2, anterior pharynx defective-1, and nicastrin [45–47]. Nicastrin recognizes and binds to the free amino terminus of the substrates [48], and presenilin cleaves type I single transmembrane proteins, such as RTKs [49]. Previous studies suggested that a conserved structural motif in the transmembrane domain of γ-secretase substrates, such as Notch, β-amyloid precursor protein and Sevenless, may be required for γ-secretase recognition [50–55]. However, so far no conserved primary sequence has been identified. Figure 3 illustrates the cleavage of ligand-bound RTKs by γ-secretase at the juxtamembrane domain to release ICD from the transmembrane domain. The ectodomain of the substrate must be shed prior to γ-secretase binding, and both the transmembrane and cytoplasmic domains must be present for subsequent cleavage.

2.3.1 ErbB Family—Of the four members in the ErbB family, the best example of cleavage is that of ErbB-4. ErbB-4 functions in embryogenesis and breast development and its expression is tissue specific (reviewed in [56]). There are two ErbB4 isoforms generated by alternative splicing, Jm-a and Jm-b. The former undergoes secretase cleavage whereas the latter does not [57]. ADMA17/TACE-regulated ectodomain shedding is enhanced when ErbB-4 is bound to heregulin [58, 59] or under protein kinase C (PKC) activation by phorbol 12-myristate 13-acetate (PMA) [60]. This leads to a 120-kDa ectodomain fragment that is released into the extracellular environment, leaving a membrane-bound 80-kDa fragment containing the transmembrane domain and ICD, called m80, which then undergoes γ-secretase cleavage to release the soluble ICD called 4ICD [61, 62]. The cleavable ErbB4 isoform is found in both normal and tumor tissues. In breast cancer, nuclear 4ICD (see later) level is negatively correlated with tumor malignancy [63, 64] and improved response to endocrine therapy but not chemotherapy [65, 66].

Other ErbB receptors also have secretase-dependent fragments. For instance, ErbB-2 ectodomain shedding is mediated by ADAM10 and MMP-1 to generate the $p95^{ErbB2}$ fragment [67]. Breast tumors resistant to TKIs, such as trastuzumab [68, 69] and lapatinib [70], and anti-oestrogen drug, toremifene [71], also express the $p95^{ErbB2}$ fragment.

2.3.2 Colony stimulating factor-1 Receptor (CSF-1R)—CSF-1R can be activated by both colony stimulating factor-1 (CSF-1) and interleukin-34 (reviewed in [72]) and is known to regulate the development and maintenance of immune cells, such as monocytes and macrophage [72], as well as regulate neuron progenitor cells, such as myeloid cells [73, 74]. Interestingly, macrophage precursors are better inducers of secretase-mediated CSF-1R

cleavage than its ligand CSF-1 [75–80]. In addition, Toll-like receptor-induced Erk activation also promotes secretase-mediated CSF-1R cleavage [81]. During macrophage activation, CSF-1R is downregulated in response to IL-2 and IL-4 stimulation via ADAM17/TACE-mediated shedding, and the cleavage is further enhanced by PMA and lipopolysaccharide [82]. The sequences within the extracellular juxtamembrane region and transmembrane domain of CSF-1R are critical for TACE-mediated shedding and γ-secretase cleavage, respectively [75, 80, 83], but exact cleavage site has not been reported.

2.3.3 Ephrin-B Receptor (Eph-B)—Erythropoietin-producing hepatoma receptors (Eph) family is considered the largest RTK family with 14 members grouped into 2 subfamilies, Eph-A (EphA1-8, Eph-A10), and Eph-B (EphB1-4, EphB6) [84]. Eph receptors are activated by ephrins. Shedding of the Eph-B1 receptor can be blocked by metalloproteinase inhibitor, GM6001, which suggests that the metalloproteinases are involved in its cleavage [85]. The ICD of Eph-B1 generated by γ-secretase cleavage has been speculated to translocate into nucleus via a putative pH-dependent nuclear localization signal in the basic amino acid cluster located within its juxtamembrane domain. However, there is no evidence for Eph-B1 nuclear localization to date [85].

Proteolytic cleavage of Eph-B2 by secretase releases its ectodomain and ICD. Interestingly, the Eph-B2 ectodomain shedding machinery is determined by a specific stimulus that determines the fate of the receptor. Ligand-induced shedding is mainly related to ubiquitinated receptor endocytosis, which is mediated by MMP-2 and MMP-9 [86]. When ligand-induced shedding occurs in the endosome, the process becomes insensitive to GM6001. In contrast, calcium influx- and N-methyl-D-aspartic acid (NMDA)-stimulated Eph-B2 cleavage on the plasma membrane without endocytosis is sensitive to GM6001 and ADAM10 inhibitor [87]. The intramembrane cleavage of Eph-B2 after shedding requires γ-secretase [88].

2.3.4. Vascular Endothelial Growth Factor 1 (VEGFR-1)—Vascular endothelial growth factor receptor (VEGFR) family binds to vascular endothelial growth factor (VEGF) and is responsible for regulating physiological and pathological angiogenesis. VEGFR-1 can also undergo ADAM10- and ADAM 17-mediated shedding to release its soluble ectodomian (sVEGFR1) [89], which has been shown to regulate VEGFR signaling by trapping VEGF. In neural retina, BACE-1-mediated VEGFR-1 shedding is required for VEGF-induced angiogenesis [90] and subsequent γ-secretase cleavage and generation of VEGFR1-ICD [90], which has been reported in leukemic cancer cells [91]. In pregnant women, increasing levels of VEGF and sVEGFR1 are positively correlated with threatened abortion [92].

2.3.5 MET—MET was discovered as TPR-MET oncogene in transformed human osteogenic sarcoma cells [93]. MET overexpression and mutation are found in many types of cancer and contribute to tumor progression, such as cell survival, invasion, and proliferation (reviewed in [94]). Ectodomain shedding of MET correlates with tumor malignant potential in many cancer cells, including non-small cell lung cancer [95, 96]. HGF, PMA, and suramin as well as MET inhibitory antibody have been shown to induce ADAM-10- and ADAM-17-mediated MET ectodomain shedding to produce a membrane–anchored 55 kDa CTF that is found in the nucleus of both normal and cancerous tissues with

ADAM-17 being the major protease [97–102]. ADAM-17-mediated MET shedding releases a soluble MET ectodomain that has been shown to promote MET/STAT3 survival signaling in MEK inhibitor-resistant *KRAS*-mutated colorectal cancer [103]. MET-CTF can further undergo ligand-independent presenilin-dependent γ-secretase cleavage to generate MET-ICD [104].

2.3.6 Tie-1—Tie-1 is an orphan receptor that supports epithelial cell survival [105] and plays important roles in both normal and pathological angiogenesis [106]. In epithelial cells, the metalloproteinase-mediated Tie-1 ectodomain shedding is stimulated by PMA, VEGF, inflammatory cytokines, and shear stress [107–109] to release a 100 kDa extracellular domain and a 45 kDa membrane-anchored CTF. Since Tie-1 forms heterodimers with Tie-2, it has been suggested that the Tie-1 shedding plays an important role in the increased binding of Tie-2 to cartilage oligomeric protein angiopoietin-1 (Ang 1) [110]. Interestingly, Tie-1 shedding to generate CTF is insensitive to metalloproteinase inhibitor TAPI-2 in MCF-7 breast cancer cells [111]. After shedding, Tie-1-CTF then undergoes γ-secretase cleavage that liberates a 43 kDa Tie-1-ICD [110]. Overexpression of Tie-1-ICD has been detected in breast cancer cells, and high levels of Tie-1-ICD in breast and colon tumors were found to correspond to cancer progression [112]. The unique functions of Tie-1 in lymphatic remodeling and maturation [113] and in breast cancer progression raise a question whether the Tie-1 fragments regulate non-canonical signaling pathways. Further studies will be needed to determine that.

2.3.7 Ryk—Unlike most RTKs, receptor-like tyrosine kinase (Ryk) does not have kinase activity due to alterations of the invariant amino acids in the catalytic domain [114, 115]. Ryk contains an extracellular Wnt inhibitory factor domain and has been shown to function as a Wnt co-receptor in axon guidance and pattern formation [116]. In 2008, Lyu *et al.* reported a 42 kDa Ryk-ICD in the cytosol and nucleus of cells in mice brain section [117]. Using a chimeric Ryk receptor and γ-secretase inhibitor DAPT, they further demonstrated that the secretase cleavage site is located within the transmembrane domain of Ryk and inhibition of γ-secretase leaves a membrane bound ectodomain-shed 45 kDa Ryk fragment.

2.3.8 ICD Formation of Other RTKS—In addition to the RTKs described above, several others have been shown to undergo protease-mediated cleavage, including the insulin receptor (InsR), insulin-like growth factor 1 receptor (IGF-1R), protein-tyrosine pseudokinase 7 (PTK7), and fibroblast growth factor receptor 3 (FGFR-3). Ectodomain shedding of InsR is induced by PKC-activated ADAM17 under PMA treatment to generate InsR-CTF, which is then cleaved by γ-secretase to produce InsR-ICD [118]. Likewise, IGF-1R also relies on PKC-activated shedding and γ-secretase cleavage to release its ICD [119]. PMA also enhances ADAM17- and γ-secretase-mediated proteolytic cleavage of PTK7 to generate two oncogenic PTK7-CTF fragments, PTK7-CTF 1 and PTK7-CTF 2 [120]. For FGFR-3, FGF1-induced shedding does not follow the traditional RIP pathway. While metalloproteinase is not essential for FGFR cleavage to generate ICD, FGFR-3 shedding does require endocytosis [121]. Table 1 lists the secretases known to date that cleave RTKs.

3. Intracellular trafficking of MRINs

3.1 Trafficking of membrane-bound MRINs

3.1.1 RTK internalization and endosomal retrograde trafficking to the Golgi and ER—

Cell surface receptors are present in many subcellular compartments, including the Golgi apparatus, mitochondria, ER, and nucleus. Upon ligand activation, RTK is rapidly internalized and translocated into the endosomal compartments for signaling, recycling, or degradation by a clathrin-mediated or -independent pathways, depending on the specific coat proteins in the membrane region that form the endocytic vesicles (reviewed in [122]). The endocytic vesicles are then sent to different subcellular compartments based on the associated cargo proteins, such as Rab proteins [123] or clathrin-binding adaptor proteins (AP) [124] (Figure 4).

Clathrin-mediated endocytosis (CME) from non-lipid raft membrane domains is the predominant mechanism for RTK internalization. Prior to RTK activation, auto-inhibition of clathrin prevents the recruitment of cytosolic adaptor protein. Upon RTK activation, clathrin recognizes specific posttranslational modifications, such as ubiquitination and acetylation, at the C-terminus of activated RTK [125, 126]. The clathrin complex then recruits cargo-specific adaptors, e.g., AP2, which can also interact with phosphatidylinositol (4,5)-biphosphate (PIP2) to bring in the phospholipids on adjacent plasma membrane to induce conformational changes that promote the formation of clathrin-coated pit through membrane curvature, clathrin polymerization, and internalization of the RTK-containing pit from the plasma membrane [127]. Moreover, CME is a highly selective process that forms only after recognition of the cargo protein sequence by AP. For example, AP2 specifically recognizes the YXXΦ and LL sequence motif ([ED]XXXL[LI]) on the cargo protein (reviewed in [128]). In EGFR, the LL motif is important for AP2 phosphorylation, which further facilitates the interaction between AP2 and EGFR, and subsequent internalization of EGFR via CME [129].

Posttranslationally modified RTKs, such as from ubiquitination, can also be internalized via a clathrin-independent endocytic pathway [130]. There are several clathrin-independent endocytic mechanisms, including phagocytosis, macropinocytosis, and lipid raft-mediated (e.g., caveolin-mediated) endocytosis, and among them, macropinocytosis and lipid raft-mediated endocytosis have been reported for RTK internalization. Macropinocytosis is a growth factor-induced and actin-mediated transient endocytic process that begins from all membranous regions, such as those of the lipid rafts, in larger vesicles containing extracellular fluid and plasma membrane-bound components. Unlike clathrin-dependent endocytosis, caveolae-mediated endocytosis does not require a specific coat protein and is usually associated with lipid raft membrane regions containing caveolin-1 protein (reviewed in [131]). Recently, Boucrot *et al.* reported a new clathrin-independent endocytic mechanism called endophilin-mediated endocytosis (FEME), which does not require AP2 or clathrin [132] and further demonstrated that FEME uses endophilin-A2 as membrane scissor to release endocytic vesicles [133]. FEME of membrane receptors, including RTKs, e.g., EGFR, MET, VEGFR, PDGFR, IGF-1R, and TrkA, requires ligand activation [132]. FEME of EGFR only occurs under high concentrations of EGF treatment and requires Cbl and

CIN85, which are RTK substrates involved in routing activated surface RTKs to the lysosome for degradation, suggesting that this newly identified pathway may be more related to downregulation of canonical RTK signaling [132].

After RTK internalization, receptors are then routed to the early endosomes, where the fate of cargo is determined. In general, RTKs can be degraded or recycled or can undergo retrograde trafficking to the Golgi apparatus (Figure 4). Although it has been reported that in EGFR is recycled after stimulation by high concentrations of ligand in A431 cells, which express high levels of EGFR with 80% of EGFR internalized [134], not all endocytic receptors are subjected to recycling or degradation. Instead, a small portion of them undergoes retrograde transport, which is the influx of protein and lipid from the cell surface to Golgi or from the Golgi to ER. The *trans* Golgi network (TGN)-targeting coat proteins, including Rab9, syntaxin 6, and GGA, guide the fusion of endosomal vesicle to the TGN [135]. Internalized RTKs, e.g., EGFR [136], c-MET [137], and fibroblast growth factor receptor (FGFR)-1 [138, 139], via CME can also be transported to the TGN for further sorting through coated vesicle transport. However, endocytic RTKs that undergo retrograde transport do not necessarily stop at the TGN as they can be further routed back to the ER and even the nucleus by COPI-mediated retrograde transport as exemplified by the Golgi-to-ER translocation of EGFR [139]. *Du et al.* recently demonstrated that inhibition of dynein or knockdown of dynein or syntaxin 6 attenuated EGFR accumulations in the Golgi apparatus and nucleus [136]. Their findings indicate that the EGFR detected in these subcellular compartments is indeed from the cell surface.

3.1.2 Nuclear trafficking of MRINs from the ER—After reaching the ER, endocytic RTKs can be further transported into the nucleus via two importin-β-mediated pathways, integral trafficking from the ER to the nuclear envelope transport (INTERNET) and integrative nuclear FGFR-1 signaling (INFS) (Figure 5) [140]. The major difference between the two is that the receptor remains membrane bound and is localized to inner nuclear membrane (INM) before nuclear translocation via INTERNET whereas FGFR-1 becomes a soluble protein after its release from ER or ER-derived membrane vesicle before translocation into the nucleus via INFS [140].

Both EGFR and ErbB-2 contain a typical NLS that attracts NLS-containing molecules for complex formation with importin-β [141]. It has been shown that EGFR and ErbB-2 are transported from the ER to the outer nuclear membrane (ONM) and then to the nuclear pore complex (NPC), where the receptors enter the INM with the help of importin-β [140, 142]. As demonstrated with digitonin-permeabilized cells, detection of importin-β in the non-nuclear extract suggested that the INTERNET mechanism depends on membrane-associated importin-β to transport EGFR and ErbB-2 from the ONM into the INM [140, 143]. Wang *et al.* further showed that Sec61β translocon is required for the release of INM-bounded EGFR into the nucleus [144]. Both EGFR and ErbB-2 contain the NLS that interacts with membrane-bound importin-β and translocate into the nucleus via the INTERNET pathway [144]. Given that NLS is conserved among most of RTKs and that nuclear translocation of another NLS-containing RTK, c-MET, also follows the INTERNET pathway (unpublished data), it is likely that INTERNET is a commonly shared mechanism for RTK nuclear

trafficking. Further investigation of the nuclear transport mechanism of other RTKs will be required to validate this notion.

Via the INFS pathway, FGFR-1 is released as soluble protein from the ER or ER-derived membrane vesicle into the cytosol through the Sec61 channel. FGFR-1 then associates with importin-β in cytoplasm before being transported into the nucleus [145]. Notably, even though FGFR-1 does not contain a consensus NLS sequence, it can still translocate into the nucleus by association with NLS-containing proteins, such as its NLS-containing ligand, FGF-2 [145].

3.2 Trafficking of RTK-ICD

RTK-ICDs are found in different intracellular compartments, including the mitochondria and nucleus, suggesting that ICDs are also subjected to intracellular transport. To avoid degradation, ICDs can either bind to other proteins, e.g., Hsp90, to enhance their stability [146, 147] or undergo posttranslational modifications by other associated proteins [148]. For example, 4ICD can be SUMOylated by protein inhibitor of activated STAT3 (PIAS3). In addition, the released ICD can bind to transcription factors, such as YAP [149], signal transducer and activator (STAT) [150], and ERβ [151], which may also stabilize the ICD for intracellular trafficking (Figure 3). The nuclear localization sequence (NLS) within the RTK-ICD or its associated proteins binds to adaptor proteins, such as importin-α and importin-β, to facilitate nuclear localization through the NPC [152, 153].

4. Functions of MRINs

4.1 ErbB family

Mutation and overexpression of ErbB receptors (ErbB-1/EGFR, ErbB-2/HER-2/neu, ErbB-3, and ErbB-4) contribute to increased malignancy of solid tumors, including non-small cell lung, breast, and colon cancers, and glioblastoma [154]. The entire ErbB family of receptors is reported to translocate into the nucleus either as holoreceptor or truncated form. In 1994, ErbB-2 was the first RTK reported to have transcriptional activity in the cell's nucleus. While nuclear localization of EGFR was first described much earlier in 1984 [155], its nuclear functions were not characterized until 2001 [156]. Below, we describe the nuclear functions that have been reported to date for each of the ErbB receptors although more studies are currently ongoing.

4.1.1 ErbB1/EGFR—EGFR nuclear translocation is triggered by various stimuli, such as EGF, radiation, anti-cancer drugs, and EGFR antibodies [16, 156, 157]. nEGFR functions as a transcription co-activator by binding to RNA helicase A and MUC1 at the AT-rich response sequence [156, 158–160] to promote cyclin-D1 gene expression. nEGFR also interacts with transcription activators E2F1, STAT3, and STAT5 to upregulate expression of target genes, such as inducible nitric oxide synthase (iNOS) [161], B-Myb [162], Aurora-A [163], cyclooxygenase-2 (COX-2) [164], c-Myc [17], thymidylate synthase (TS) [165], and BCRP [17, 25]. By increasing their expression, nEGFR promotes cell proliferation, inflammation, and genome instability as well as tumor progression.

Several anti-EGFR drugs such as erlotinib, gefitinib, afatinib, and monoclonal antibody cetuximab have been approved by the FDA for cancer treatment [166]. As alluded to above, nEGFR has been shown to contribute to the development of acquired resistance to radio-, chemo-, or targeted therapies [16, 24, 25, 167–169]. For example, phosphorylation of EGFR at Y1101 promotes EGFR nuclear translocation and enhances nEGFR-mediated iNOS and B-Myb transcription in cetuximab-resistant cells [170]. Aside from its role as a transcription co-activator, nEGFR also activates DNA replication and repair. Specifically, nEGFR binds to and phosphorylates proliferation cell nuclear antigen (PCNA) at Y221 residue to stabilize PCNA, which subsequently enhances cell proliferation [171], inhibits DNA mismatch repair, and promotes genome instability [172]. EGFR also interacts with ataxia telangiectasia mutated (ATM) in the nucleus after ionizing radiation and mediates DNA damage response by phosphorylating ATM at Y370 to promote DNA repair and cell survival [18]. nEGFR also phosphorylates histone H4 at Y72, which then modulates K20 methylation of histone H4 to promote DNA synthesis and repair [173]. Moreover, a positive correlation was reported between phosphorylation of DNA-dependent protein kinase (DNA-PK) and nEGFR expression after irradiation. While there is no evidence to suggest that DNA-PK is a direct substrate of nEGFR, these findings point to the importance of nEGFR in DNA damage repair [174–176]. Figure 6 illustrates various functions of nEGFR.

Besides the nEGFR holoreceptor, some of the EGFR variants are also detected in the nucleus. EGFRvIII and mLEEK have been shown to translocate into the nucleus to regulate cellular responses. In glioblastoma, nuclear EGFRvIII regulates COX-2 and Bcl-XL transcription through its interaction with STAT3 [164] and STAT5b [177]. Nuclear mLEEK has been reported to regulate transcription of ER chaperon protein GRP78 under ER stress [32].

4.1.2 ErbB-2/HER-2/neu—Although ErbB2 itself is not sufficient to induce internalization because it is an orphan receptor that lacks a well-defined ligand, nuclear trafficking of ErbB-2 has been reported via the INTERNET pathway [140, 141, 178]. Ubiquitination of ErbB-2 (reviewed in [179]) or heterodimerization of ErbB-2 with other ErbB members, such as EGFR [180], facilitates its internalization.

Nuclear localization of ErbB2 was first reported more than two decades ago [181]. Similar to EGFR, ErbB-2 can also form a complex with STAT3 to transcriptionally upregulate COX-2 [178], cyclin D1 [182], and ribosomal RNA [183]. It has been shown that the progesterone receptor-induced nuclear ErbB-2/STAT3 complex promotes breast cancer cell growth [182]. In addition, nuclear ErbB-2 also phosphorylates atypical histone macro-H2A1.2 to promote its own gene transcription, resulting in ErbB-2 overexpression and cell proliferation in cancer cells [184]. Aside from transcriptional regulation, nuclear ErbB-2 is reported to phosphorylate cell division cycle protein 2 homolog (Cdc2) Y15, leading to inhibition of Cdc2 and resistance to taxol-induced apoptosis in breast cancer patients [185].

ErbB-2 is also present in nucleus in the truncated form due to alternative translation initiation that generates two ErbB2-CTF variants, 611-CTF and 687-CTF. Interestingly, 611-CTF is a membrane-associated fragment while 687-CTF is not because it lacks the transmembrane domain. Although the ErbB-2 fragments are known to interact with and

stabilized by Hsp90, the underlying nuclear trafficking mechanisms are not well understood (reviewed in [179]). Both 611-CTF and 687-CTF are detected in the cytoplasm as well as the nucleus. The 611-CTF variant is hyperactive and more correlated with tumor progression (reviewed in [186]). Studies have indicated that 611-CTF contributes to cell migration and breast cancer cell metastasis by phosphorylating cortactin, a cytoskeletion-binding protein [187], and by promoting transcription of metastasis-related genes, such as *MET*, *MMP1*, and *IL11*, and those that express integrins and Eph receptors [188].

4.1.3 ErbB-3—Due to sequence alteration in its tyrosine kinase domain, the kinase activity of ErbB-3 is lower than that of other ErbB receptors [189]. High expression of nuclear ErbB-3 has been observed in prostate cancer cells as well as in tumor tissue of prostate cancer patients [190–193]. In normal tissues, ErbB-3 is mainly located on the cell surface and in the cytoplasm. Interestingly, immunohistochemistry staining revealed that low nuclear ErbB-3 expression is correlated with cancer cell survival and recurrence [191].

Different from ErbB-1 and ErbB-2, nuclear trafficking of ErbB-3 begins by macropinocytosis instead of clathrin-independent endocytosis [194]. Internalization of ErbB3 is triggered by neuregulin and inefficiently translocated to the lysosome for degradation (reviewed in [195]). Nuclear localization of the ErbB-3 variant ($ErbB3_{80kDa}$) was recently reported by Andrique *et al.* [196] who demonstrated that nuclear $ErbB3_{80kDa}$, which lacks kinase activity, corresponds to the intracellular domain of the receptor. Although $ErbB3_{80kDa}$ may possess little kinase activity, it binds to and regulates the cyclin D1 promoter, which promotes transcriptional activation and cell proliferation [196]. In addition, a 50 kDa nuclear ErbB3 (nuc-ErbB3) variant that regulates transcriptional activity and distribution of Ezrin was reported to contribute to myelination of Schwann and glial cells [197, 198].

4.1.4 ErbB-4—As described in **Section 2.3.1**, 4ICD is generated by secretase cleavage. The proteolytic processing of ErbB4 is functionally important as 4ICD translocates into nucleus and binds to regulators that modulate transcription, including transcription factors YAP [149], ERβ [151] and STAT5A. In astrocytes, 4ICD forms a complex with corepressor N-CoR and TGF-β-activated kinase 1-binding protein 2 (TAB2), which then translocates into the nucleus to repress gene expression [147]. Nuclear 4ICD has also been reported to regulate β-casein gene expression that is crucial to milk production [199] and fetal lung maturation [150]. In addition, colocalization of 4ICD and HIF-1α has been reported, and their interaction in the nucleus may promote HIF-1α stability and signaling [200].

4.2 Other MRINs

4.2.1 FGFR Family—FGFRs regulate cellular processes including cell proliferation, differentiation, and survival, and thus are important in cancer progression [201]. Traditionally, the FGFR family contains four members–FGFR-1, FGFR-2, FGFR-3 and FGFR-4. Recently, FGFR-5, also known as FGFRL1, was added to this family based on its interaction with FGFR ligands. The conventional FGFR family is highly conserved in sequence homology whereas FGFR-5 lacks the TK domain.

Nuclear translocation of FGFR-1 holoreceptor by ligand stimulation has been reported in many types of tumor tissues and cancer cell lines (reviewed in [202]). Internalization of FGFR-1 is facilitated by the FGF-2-activated heparin sulfate proteoglycan, syndecan 4, via macropinocytosis [203]. Nuclear transport of FGFR-1 occurs via an importin-β-mediated INFS mechanism and has been shown to promote cell proliferation by activating transcription coactivator cAMP response element-binding (CREB)-binding protein to enhance gene transcription (reviewed in [145, 204]). In addition, Hu *et al*. demonstrated that nuclear FGFR-1 can also translocate into the nucleus from the Golgi directly after protein synthesis [205]. The authors also showed that FGFR-1 phosphorylates ribosome S6 kinase 1 (RSK1), a modification that is critical for RSK1-mediated transcriptional activation of c-Fos, CREB, estrogen receptor, and Iκ Bα as well as histone H3 remodeling [205].

Nuclear FGFR-2 has been shown to regulate mammary gland development through interaction with STAT5. Thus, FGFR-2 is considered to play an important role in mammary tumor growth. Indeed, expression of nuclear FGFR-2 in breast cancer patients is corrected with poor prognosis [206, 207]. FGFR3-ICD, located in both the cytosol and nucleus, is generated by secretase cleavage and released as a soluble protein [121, 208]. FGFR3-ICD is also the only FGFR ICD reported in the nucleus to date. In malignant breast cancer tissues, increased nuclear localization of FGFR3 was observed [209]. More studies are needed to further delineate the physiological and/or pathological role of nuclear FGFR3-ICD.

4.2.2 VEGFR Family—The VEGFR family is composed of three members, VEGFR-1/Flt-1, VEGFR-2/KDR/Flk-1, and VEGFR-3/Flt-4. VEGFR-1 and VEGFR-2 bind to VEGF-A while VEGF-3 binds to VEGF-C and VEGF-D. The biological functions of these three members are distinctively different: VEGFR-1 mainly functions in non-epithelial cells; VEGFR-2 plays an important role in epithelial cells; and VEGFR-3 mediates lymphaogiogenesis (reviewed in [210]).

VEGFR-1 holoreceptor can be found on the membrane, cytoskeleton, and nucleus [211]. Nuclear VEGFR-1 predominantly co-localizes with lamin A/C in the nuclear fraction in breast cancer cells without ligand stimulation and is correlated with cell survival [212]. However, more studies are needed to clarify the function and identify the substrate of nuclear VEGFR-1 holoreceptor. VEGFR1-ICD is generated and detected in the cytoplasm when cells are exposed to pigment epithelium-derived factor (PEDF) in the presence of VEGF. PEDF is also responsible for VEGF-induced VEGFR phosphorylation in addition to VEGFR cleavage [213], suggesting that VEGFR1-ICD generation may be related to downregulation of VEGFR-1 canonical signaling. Nuclear translocation of VEGFR1-ICD has been reported to function in angiogenesis [211, 213], and VEGFR1-ICD without its TK domain can still stimulate normal embryonic development and angiogenesis [214], suggesting that the kinase activity is not crucial for its nuclear function and a possible role of VEGFR1-ICD as a transcription regulator. Further investigation will be required to validate the potential function of VEGFR1-ICD as a transcriptional coactivator.

VEGFR-2 translocates into nucleus under VEGF stimulation in endothelial cells, and has been reported to form a complex with tissue transglutaminase II to mediate this process [215]. Studies have also indicated that nuclear VEGFR2 holoreceptor promotes its own

transcription by binding to the transcription factor Sp1 [216] and functions in endothelial wound healing [217]. Still, there may be more functions of nuclear VEGFR-2, pending further investigations.

4.2.3 MET Family—The MET receptor, also known as c-MET or hepatocyte growth factor (HGF) receptor, is responsible for HGF-induced signaling pathways. Overexpression of MET is detected in many cancer types, including non-small cell lung, breast, colorectal, liver, and ovarian cancers. Moreover, overexpression of MET not only correlates to tumor malignancy but also contributes to acquired resistance to EGFR TKIs (reviewed in [94].) In liver SK-HEP-1 cell line, Gomes *et al.* demonstrated that MET translocates from the plasma membrane to the nucleus in response to HGF stimulation through Gab-1 and importin-β to induce inositol 1,4,5-triphosphate (InsP3) formation in the nucleus. This in turn activates InsP3-dependent calcium release into the nucleoplasm to promote cell proliferation [218]. Androgen deprivation in prostate cancer cells has been reported to induced nuclear accumulation of MET holoreceptor, which contributes to castration-resistant prostate cancer progression through upregulation of SOX9 and activation of the β-catenin signaling pathway [219].

MET intracellular fragments have also been observed in the nucleus. Matteucci *et al.* reported that nuclear translocation the MET C-terminal fragment, which possesses trans-activating activity that promotes gene transcription in malignant breast cancer cells, does not require ligand stimulation [220, 221]. However, it is not clear from their study whether γ-secretase is essential for the formation of the MET C-terminal fragment. Later, Xie *et al.* reported their discovery of nuclear MET-ICD in prostate cancer cells and found that its level decreased in response to γ-secretase inhibitor [219]. In addition, based on the molecular weight of the MET-ICD identified, their findings indicate that the MET C-terminal fragment previously described by Matteucci *et al.* was indeed MET-ICD.

The other member of the MET family, Ron, which binds to hepatocyte growth factor-like protein/macrophage stimulating-protein, is mainly expressed on macrophages and epithelial cells. Similar to MET, overexpression of Ron in various cancer types, including breast, colon and pancreatic cancers, is correlated with poor prognosis and metastasis [222]. In response to serum starvation, Ron translocates into the nucleus, which requires importin and heterodimerization with EGFR. High levels of nuclear Ron have been observed in bladder cancer cells and primary bladder tumors [223]. Hypoxia can also trigger nuclear translocation of Ron to transcriptionally regulate c-JUN and HIF-1α in cancer cells [224]. Moreover, nuclear Ron associates with the chromatin, and potential target genes of nuclear Ron identified are related to several stress-responsive networks [224].

4.2.4 Trk Family—There are three RTKs in this family, TrkA, TrkB and TrkC. Trk is activated by neurotrophins, nerve growth factor, and brain-derived neurotrophic factor, and Trk signaling regulates the development and function of the neural system, including cell survival, proliferation, neural precursors differentiation, growth and patterning of axons and dendrites [225]. Nuclear TrkA has been detected in PC12 rat neuroblastoma cells under NGF stimulation [226] as well as in hepatocytes and activated stellate cells [227]. However, the nuclear function of TrkA is currently unknown.

4.2.5 ROR Family—Receptor tyrosine kinase-like orphan receptor (ROR) is expressed during development in many tissue types and is functionally related to Trk and muscle specific kinase (MuSK). Mutational studies of ROR indicated that it plays important roles in cell migration and cell polarity determination as ROR-deficient mice have defective heart and bone formation (reviewed in [228]). In normal development, ROR is regulated by Wnt5a [229] Interestingly, overexpression of ROR correlates with tumorigenesis [230]. Of the two ROR family members, ROR1 and ROR2, only ROR1 is reported to have nuclear localization, which requires its juxtamembrane domain. In the nucleus, ROR1 functions in cell migration and cytoskeleton regulation [231, 232].

4.2.6 PDGFR Family—There are five members in platelet-derived growth factor receptor (PDGFR) family, PDGFRα, PDGFRβ, colony stimulating factor-1 receptor (CSF-1R)/FMS, KIT/SCFR, and FLT3. The functions and ligands for each member are different. PDGFRα and β are responsible for PDGF-induced cell replication, migration, and survival signaling of myofibroblasts during fibrotic disease pathogenesis [233]. CSF-1R mainly functions in regulating monocytes and macrophages as well as in trophoblast implantation and breast development. KIT is a stem cell factor receptor (SCFR), and the deregulation of KIT is related to mast cell proliferation disease and neoplasms [234]. So far, only PDGFRα and CSF-1R have been reported to translocate into the nucleus. Studies have indicated that nuclear PDGFRα in alveolar fibroblasts plays a role in early embryonic and lung development in mouse model [235, 236]. However, further investigation is needed to determine whether PDGFRα is present in the nucleus in humans and identify its function.

Recently, Barbetti *et al*. reported nuclear translocation of the CSF-1R holoreceptor and its functions in breast cancer [237]. In this study, they showed that nuclear CSF-1R was present only in breast cancer cells but not in fibroblasts or macrophages. Moreover, they reported a transcriptional regulatory role of nuclear CSF-1R in promoting the expression of CSF-1 and cell proliferation genes, such as *CCND1*, *MYC*, and *JUN* [237]. In addition to the CSF-1R nuclear holoreceptor, CSF-1R ICD is also detected in nucleus but its function is still not well understood. Based on its stimuli, it has been speculated that cleavage of CSF-1R may be important during macrophage activation [81].

4.2.7 Insulin Receptor Family—Members of this family include the insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and insulin receptor-related protein (InsRR). In normal tissues, these receptors promote metabolism, cell proliferation, differentiation, and survival. However, there is accumulating evidence to suggest that most cancers highly express these receptors to promote tumorigenesis (reviewed in [238]).

Nuclear IGF-1R has also been detected in many types of cancers with high proliferation rate, including lung, breast, and prostate cancers, and hepatocyte carcinoma [239]. IGF-1-activated IGF-1R can be internalized through either caveolin- or clathrin-dependent endocytosis. However, nuclear translocation of IGF-1R is blocked by clathrin inhibitors but not by caveolin depletion, suggesting that nuclear transport of IGF-1R is CME dependent [239]. Moreover, ligand-dependent SUMOylation of IGF-1R further elevates its nuclear accumulation [240]. Results from ChIP-Seq analysis indicated that nuclear IGF-1R interacts with chromatin, and thus it may also regulate gene transcription [240]. Nuclear translocation

of IGF-1R and its association with chromatin can be blocked by IGF-1R inhibitor [239]. IGF-1-induced nuclear InsR/IGF-1R heterodimer has been reported in corneal epithelial cells [241], and the target genes of the nuclear InsR/IGF-1R are involved in cell proliferation and cell cycle control as well as apoptosis. In hepatocyte carcinoma, IGF-1R nuclear translocation increases when cells are treated with gefitinib, and correlated with increased stem cell marker CD133, suggesting that nuclear IGF-1R may be involved in acquired drug resistance in hepatocyte carcinoma [242]. Interestingly, the extracellular α-subunit of IGF-1R (IGF-1Rα) but not the intracellular β-subunit accumulated in the nucleus following IGF treatment in Graves' disease fibroblasts [243]. While the authors demonstrated that ADAM17 is required for nuclear translocation of IGF-1R, nuclear IGF-1Rα is not the typical ICD fragment observed for other RTKs, and it is not clear why this ligand binding subunit is transported into nucleus instead of the intracellular domain. More studies would be required to understand the intracellular trafficking mechanism of IGF-1Rα.

4.2.8 Eph Family—Because Eph and ephrin are both membrane bound, Eph signaling is activated via cell-cell interaction. However, the signaling outcome differs depending on the cell type and microenvironment [84]. Eph is responsible for embryonic development, disease pathogenesis, and tissue homeostasis.

Cytosolic Eph-B2 ICD (EphB2/CTF2) is generated by γ-secretase cleavage and is reported to phosphorylate and promote tyrosine phosphorylation of NMDA receptor and its cell surface localization [244]. Studies by immunohistochemical staining detected Eph-B2 in the nucleus of prostate cancer cells after demethylation agents, but whether it exists as a holoreceptor or truncated form and what functions are carried out by nuclear Eph-B2 have yet to be determined [245]. Eph-A4 has been reported in both the cytoplasm and nucleus of osteoblastic cells, but the size and function of nuclear Eph-A4 is not known [246].

4.2.9 Ryk Family—Wnt pathway components, Ror and 14-3-3, regulate nuclear localization of Ryk [247]. The function of Ryk signaling is parallel to that of the classical Wnt ligand, Frizzled [248]. Proteolytic cleavage of Ryk by γ-secretase is essential for Wnt-dependent neuronal differentiation [116, 248], and stabilization of Ryk-ICD by Cdc37 is necessary to prevent its degradation. Under Wnt stimulation, Ryk-ICD translocates into nucleus [117, 146] and is essential in neuronal differentiation [117].

4.2.10 PTK Family—PTK7 plays an important role in vertebrate tissue morphogenesis. As mentioned above, PTK7 is cleaved by ADAM17 and γ-secretase. Specifically, PTK-CTF2 has been shown to translocate into the nucleus, which promotes cell proliferation, migration, and colony formation [120]. Studies have indicated that while both PTK7-CTF 1 and 2 reduce the levels of phosphorylated c-Jun, phosphorylation of CREB and ATF1 is enhanced, suggesting that PTK7-CTFs may be involved in CREB/ATF1 regulation via the RAS-ERK pathway [249]. Moreover, PTK7-CTFs are present only in tumor tissues and correlated with cell motility and metastasis in colorectal cancer [250].

4.2.11 TAM Family—The TAM family is composed of Tyro3, Axl, and Mer receptors. Overexpression of members of the TAM family has been reported for many types of human cancer. For example, Axl and Mer are considered to be proto-oncogenes in colon cancer

[251]. Growth arrest-specific gene 6 activates TAM receptors to promotes cancer cell proliferation and survival *in vitro* [252]. Mer contains a conventional NLS, and its glycosylated form has been detected in the nucleus [253]. Long-term ligand exposure induces the production of partially N-glycosylated Mer, which is associated with decreased and increased levels of plasma membrane and nuclear Mer, respectively. Nuclear Mer also exists as a soluble or chromatin-associated form, depending on the extent of its glycosylation [253]. These findings suggest that nuclear Mer may participate in transcriptional regulation in response to ligand stimulation.

5. Conclusion

In this review, we summarize the molecular mechanisms of intracellular RTK formation, trafficking, and their reported functions. Based on the current information, more studies are needed to better characterize the intracellular RTKs. For example, the retrograde trafficking mechanism for both RTK-ICD and membrane-bound RTK is not fully understood, and the underlying molecular machineries are only shown for several receptors. In addition, breakdown of RTKs via the canonical RTK degradation pathway also requires RTK internalization and cytosolic trafficking, and therefore, it may be difficult to distinguish RTK fragments detected in the cytosol from those intended to carry out non-canonical functions in other subcellular compartments. Most of the non-canonical functions are gleaned from studies of the FGFR and ErbB family. While transcriptional regulation seems to be the major function of nuclear RTKs (Table 2), their target genes have not been fully identified.

RTK internalization is a common process in various cell types, but the effects of internalization differ. Normally, in most of cells, RTK internalization is more related to regulation of the magnitude of signaling by either receptor recycling or degradation. However, the internalized RTK also travels through retrograde transport to other subcellular compartments, such as mitochondria and nucleus, where it interacts with non-canonical substrates to regulate the signal specificity. Nuclear RTK is frequently found in highly proliferative tissues. For example, nEGFR is present in regenerating tissues, such as the liver and uterus of pregnant individual, cancer cells, and primary tumor specimens [156, 254–260], and nuclear IGF-1R is detected in many types of highly proliferative cancer [239]. There are also certain stimuli, e.g., ionizing radiation, cisplatin treatment, hypoxia, and some EGFR TKIs, that have been shown to enhance translocation of EGFR into the nucleus, where it promotes aberrant signaling, leading to increased cell proliferation and survival, and resistance to apoptosis and environmental stress [16, 24, 25, 167–169].

It is worthwhile to mention that although a large number of RTKs are internalized, only a small number travel to the nucleus. For example, ~80% of EGFR is internalized [134], but only ~2–6% of EGFR translocates into the nucleus following ligand stimulation [171]. In spite of that, the non-canonical substrates of nuclear RTK are critical regulators, e.g., transcriptional activators and co-activators, which can significantly amplify nuclear RTK signaling. As a result, a few nuclear localized RTK can have a significant impact on cell proliferation and survival.

In this review, we described the translocation of many RTKs into subcellular compartments, especially the nucleus as holoreceptors or intracellular fragments and their roles or substrates in non-canonical RTK signaling, which is much less known compared with the canonical RTK signaling. There is increasing evidence that points to the role of non-canonical RTK signaling in disease progression and therapeutic resistance [16, 21]. Thus, more in-depth investigation on our understanding of ICD formation as well as nuclear trafficking pathways will be required to develop more efficient targeted therapies as the RTK holoreceptors or ICD fragments are not efficiently targeted by current clinically used TKIs.

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Abbreviations

ADAM	a disintegrin and metalloproteinase
AP	adaptor proteins
ATM	ataxia telangiectasia mutated
BACE	aspartic proteases
Cdc2	cell division cycle protein 2 homolog
CME	clathrin-mediated endocytosis
COPI	coat protein 1
COX-2	cyclooxygenase-2
CREB	cAMP response element-binding protein
CSF-1R	colony stimulating factor-1 receptor
C-term	carboxyl terminus
CTF	carboxyl-terminal fragment
DNA-PK	DNA-dependent protein kinase
EGFR	epidermal growth factor receptor
Eph	Erythropoietin-producing hepatoma receptors
ER	endoplasmic reticulum
FEME	endophilin-mediated endocytosis
FGFR	fibroblast growth factor receptor
HGF	hepatocyte growth factor
ICD	Intracellular domain

IGF-1R	insulin-like growth factor 1 receptor
INFS	integrative nuclear FGFR-1 signaling
INM	inner nuclear membrane
iNOS	inducible nitric oxide synthase
InsP3	inoaitol 1,4,5-triphosphate
InsR	insulin receptor
INTERNET	integral trafficking from the ER to the nuclear envelope transport
mLEEK	mini-LEEK
MMP	matrix metalloproteinase
MRIN	membrane receptor in nucleus
MuSK	muscle specific kinase
nEGFR	nuclear EGFR
NGF	neurotrophins-nerve growth factors
NLS	nuclear localization sequence
NMDA	N-methyl-D-aspartic acid
NPC	nuclear pore complex
ONM	outer nuclear membrane
PCNA	proliferation cell nuclear antigen
PDGFR	platelet-derived growth factor receptor
PEDF	pigment epithelium-derived factor
PIP2	phosphatidylinositol (4,5)-biphosphate
PKC	protein kinase C
PMA	phorbol 12-myristate 13-acetate
PTK7	protein-tyrosine pseudokinase 7
RIP	regulated intramembrane proteolysis
ROR	receptor tyrosine kinase-like orphan receptor
RSK1	ribosome S6 kinase 1
RTK	receptor tyrosine kinase
Ryk	receptor-like tyrosine kinase
STAT	signal transducer and activator
TACE	tumor necrosis factor-α-converting enzyme
TGN	*trans* Golgi network

TK	tyrosine kinase
TKI	tyrosine tyrosine kinase inhibitor
Trk	tropomyosin receptor kinases
VEGF	vascular endothelial growth factor
VEGFR	vascular vascular endothelial growth factor receptor

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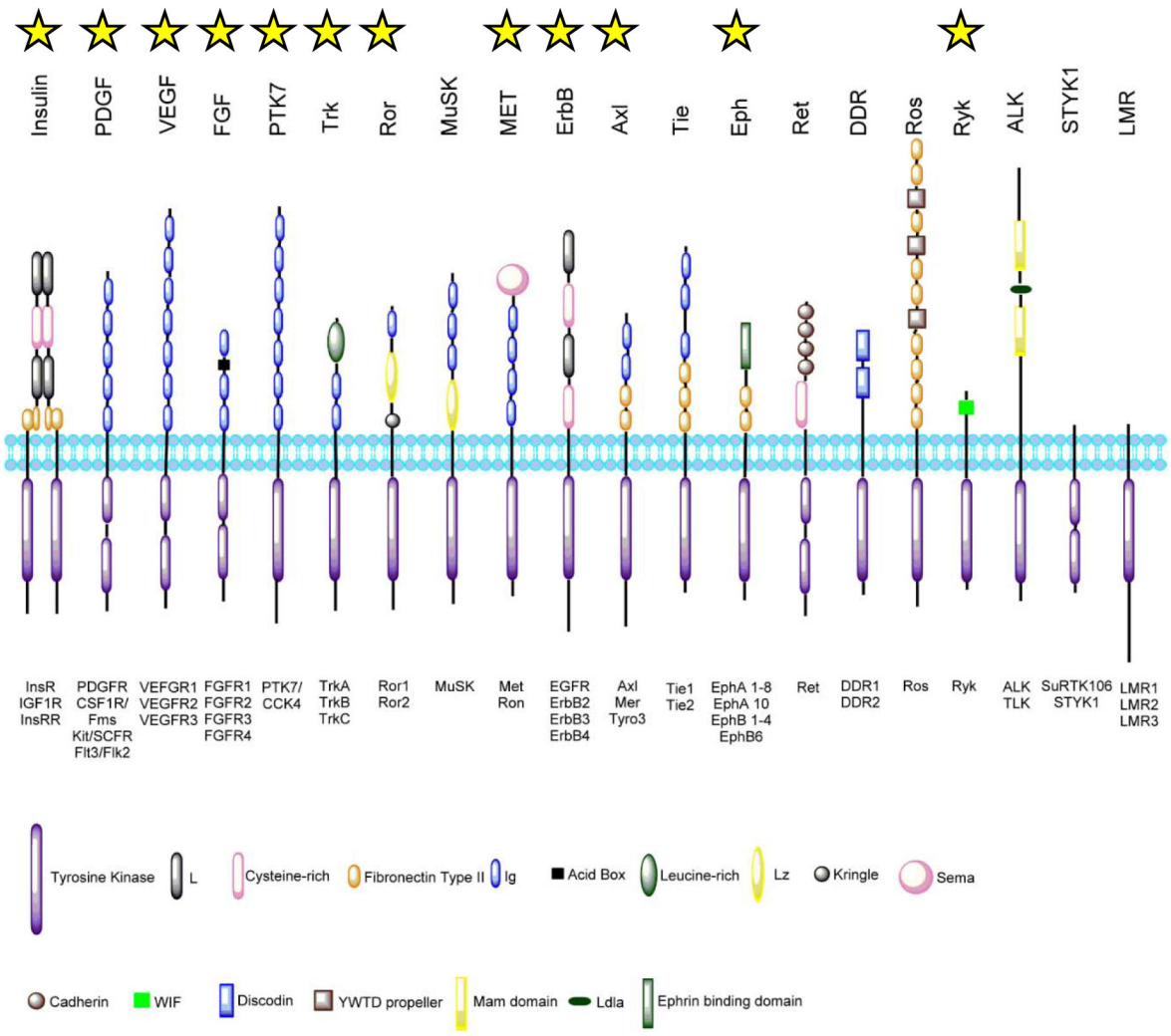

Figure 1. Receptor tyrosine kinase subfamilies

Among receptor tyrosine kinases, 20 subfamilies are identified in human genome. Those that contain receptor reported as MRIN are marked by a yellow star. The subfamilies are illustrated here with their extracellular domain structures marked accordingly in the key. The intracellular tyrosine kinase domain is shown as purple rectangle. The family members are noted below each subfamily. The lipid bilayer represents the plasma membrane, and the schematic here does not reflect the actual scale. (This figure is modified from the work of Lemmon and Schlessinger [3]).

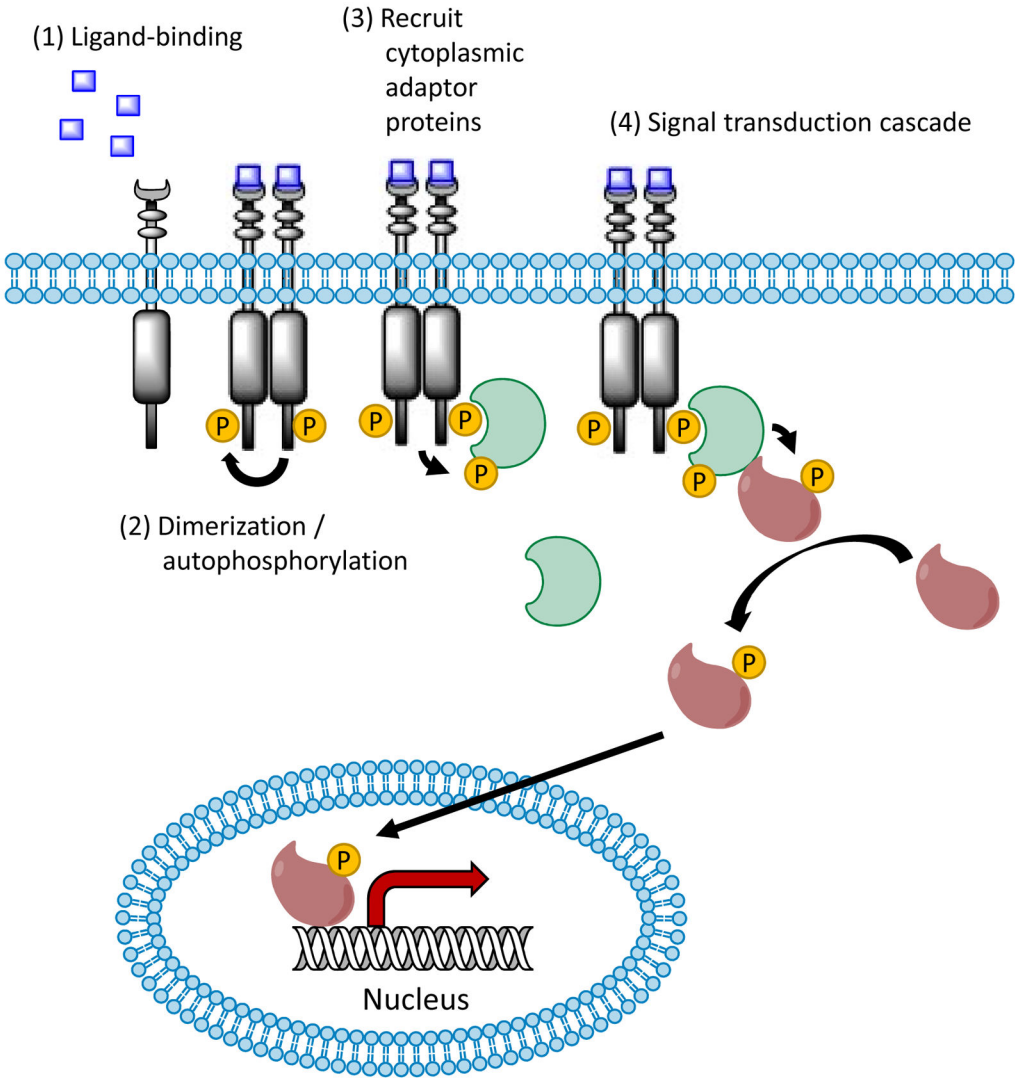

Figure 2. Canonical RTK signaling cascade

The canonical RTK signaling begins with (1) the receptor binding with its ligand. (2) The receptor then undergoes oligomerization and *trans* auto-phosphorylation. (3) The phosphor-tyrosine residues serve as docking sites for the secondary messenger proteins containing either SH2 and/or PTB domain (green) that are subjected to phosphorylation by the RTK. (4) The secondary messenger proteins recruit and activate downstream proteins (burgundy) which serve as envoys delivering signals into the nucleus to regulate gene transcription.

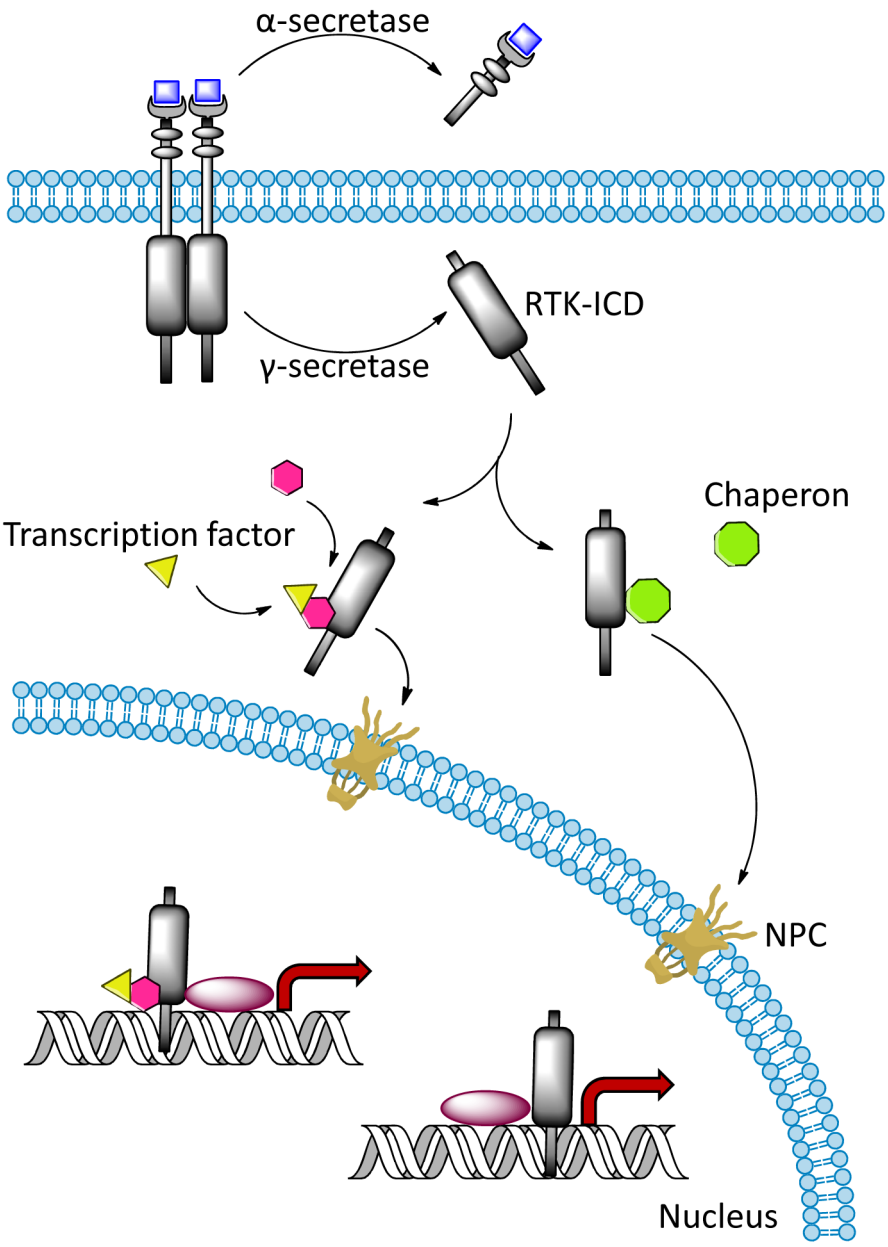

Figure 3. Protease-dependent RTK-ICD formation and intracellular domain trafficking

After activation, the RTKs are subjected to α-secretase mediated shedding to free the ectodomain before intracellular domain (ICD) is released into cytoplasm by γ-secretase cleavage. The ICDs are stabilized and guided across the cytoplasm and into nucleus through nuclear pore complex (NPC) by binding to transcription factors or chaperons. ICDs have been reported to act as transcriptional coactivators.

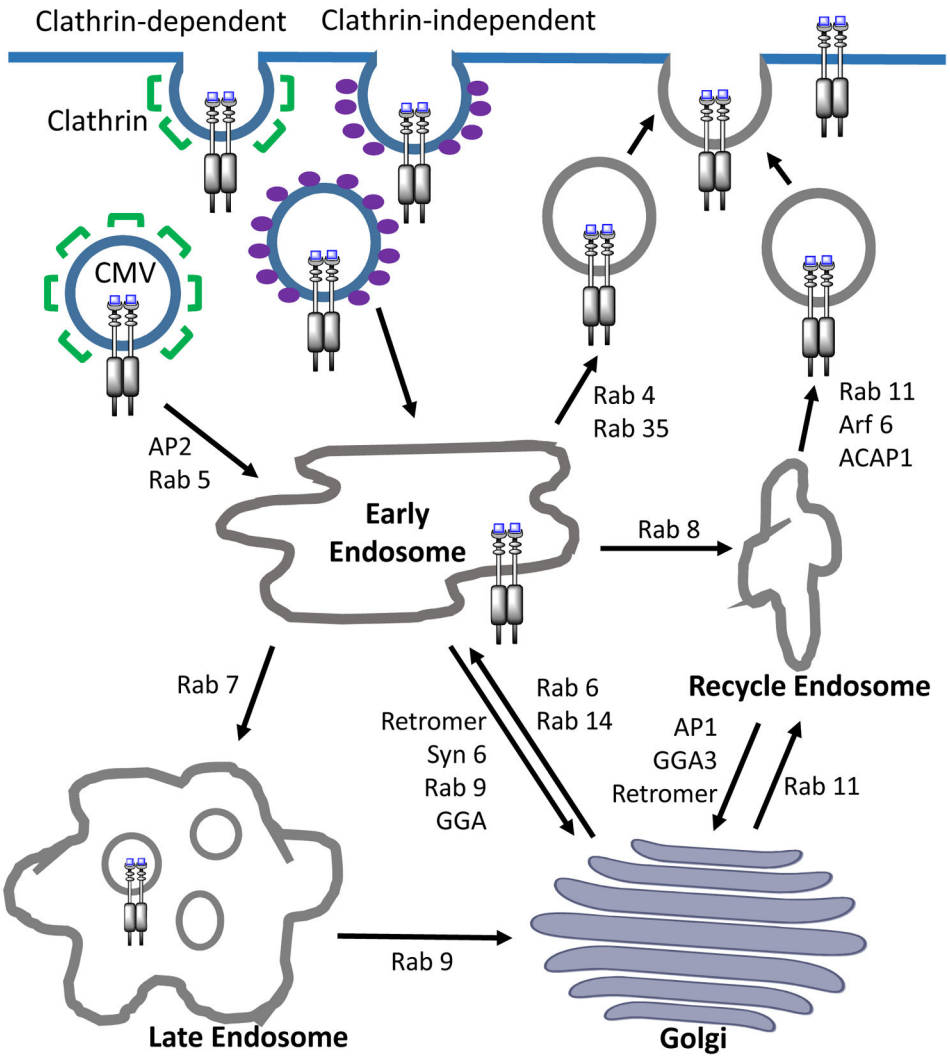

Figure 4. Endosomal vesicle trafficking of internalized RTK

RTKs are internalized through either clathrin-dependent or clathrin-independent pathways. In clathrin-dependent endocytosis mechanism, the internalized membrane vesicle is coated with clathrin (green). Meanwhile, caveolin-mediated endocytosis, which is the main clathrin-independent RTK endocytic mechanism, is initiated at the membrane region that contain caveolin-rich lipid raft (purple). The endocytic vesicles from both pathways are sent to early endosome for sorting. Based on the component of coating proteins, the vesicles are then transported to different endosomal components, including recycle endosome, late endosome and *trans* Golgi network. Several important coating proteins that direct vesicle transport are shown, including Rab proteins, clathrin-dependent adaptor proteins (AP), retromer, syntaxin 6 (Syn 6), and Golgi-associated, gamma adaptin ear containing, ARF binding protein (GGA).

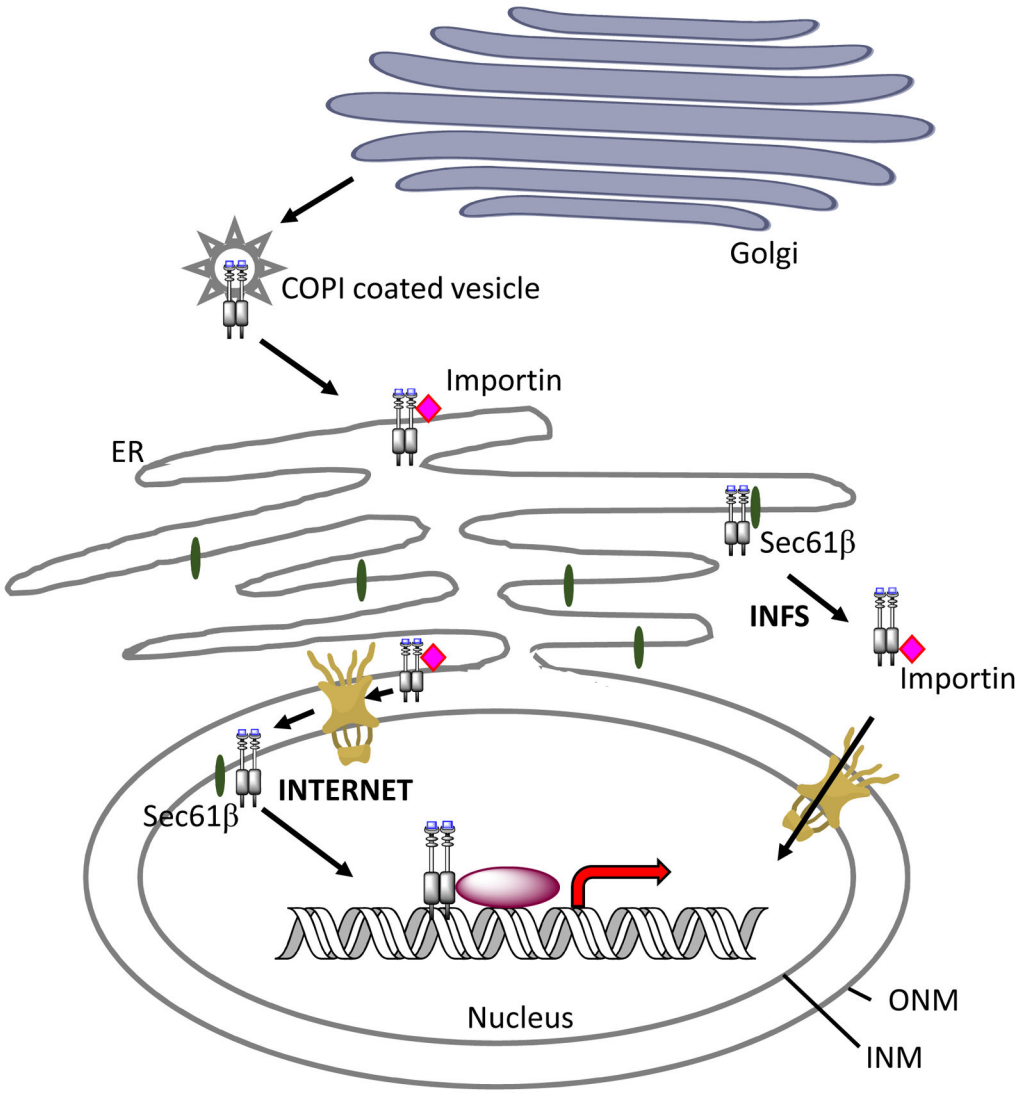

Figure 5. Retrograde and nuclear transport mechanisms of membrane-bound RTKs

RTKs are transported from Golgi to ER in COPI-coated vesicles via the retrograde pathway. The ER-to-nuclear transport of RTKs is mediated by two pathways, INFS and INTERNET. Via INFS pathway, the RTK is pumped through the Sec61 complex into the cytosol where it binds to cytosolic importin complex and transported into nucleus by the importin-NPC interaction. Via the INTERNET pathway, the RTK is trafficked along ER, translocated from the ONM to INM through the NPC by binding to ER-associated importin, and released from the INM by the Sec61 complex into the nucleoplasm. Nuclear localized RTK interacts with transcription factors and functions as transcriptional regulator.

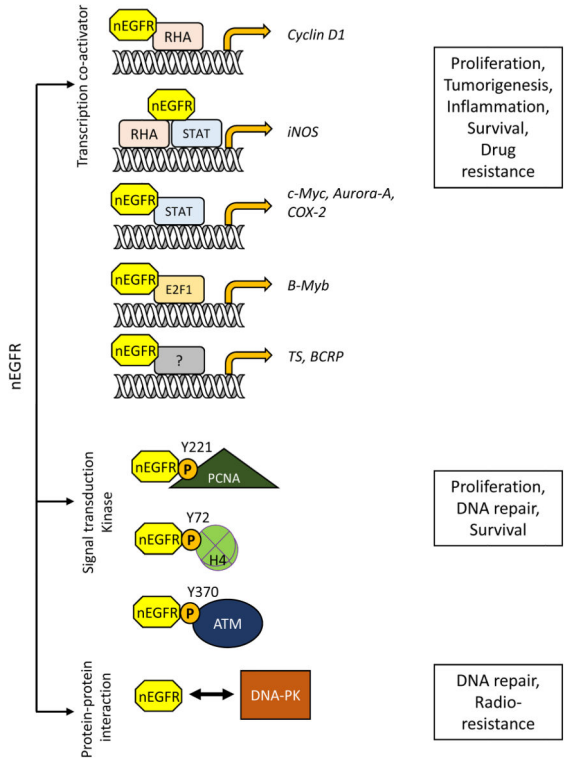

Figure 6. Functions of nuclear EGFR

Nuclear EGFR (nEGFR) has different roles in regulating cellular fate. (1) nEGFR can function as a transcription co-activator by interacting with different transcription factors, such as RNA helicase A (RHA), STAT, and E2F1, to promote target gene transcription. Elevated levels of these genes result in cell proliferation, tumorigenesis, and inflammation and are also correlated with drug resistance. (2) nEGFR phosphorylates its substrates, such as PCNA, histone H4, and ATM, to promote cell proliferation and DNA repair. (3) nEGFR also interacts with DNA-PK to increase DNA repair, leading to the development of radioresistance.

Table 1

Ectodomain shedding and proteolytic cleavage of RTKs

RTK	Ectodomain shedding	Ref.	Secretase cleavage	Ref
CSF-1R	**ADAM17** Enhanced by CSF, PMA and lipopolysaccharide	[75, 82, 83]	**γ-secretase** Poorly induced by ligand. Induced by PMA, macrophage precursors and Toll-like receptor induced Erk activation	[75–81, 83]
DDR1	Enhanced by type I collagen	[261]		
Eph-B1	**MMP** Enhanced by PMA, blocked by GM6001	[85]	**γ-secretase**	[85]
Eph-B2	**MMP-2, MMP-9** Mediated by MMP in response to ligand. Insensitive to MMP inhibitor if receptor locates in endosome **ADAM10** Mediated by ADAM10 in response to ligand, calcium influx and NMDA stimulation	[86, 87]	**γ-secretase**	[87, 88]
ErbB-2	**ADAM10, MMP-1** Enhanced by PMA, trastuzumab, pervanadate and toremifene	[67, 69, 71]		
ErbB-4	**ADAM17** Enhanced by binding with heregulin or by PMA-activated PKC	[58–60]	**γ-secretase**	[61, 62]
FGFR-3	Enhanced by FGF1 Requires endocytosis	[121]		
IGF-1R	Enhanced by PKC	[119]	**γ-secretase**	[119]
InsR	**ADAM17** Enhanced by PMA	[118]	**γ-secretase**	[118]
MET	**ADAM10, ADAM17** Enhanced by HGF, PMA, suramin and MET antibody	[97–102]	**γ-secretase**	[104]
PTK7	**ADAM17** Enhanced by PMA	[120]	**γ-secretase**	[120]
Ryk			**γ-secretase**	[117]
Tie-1	Enhanced by PMA, VEGF, inflammatory cytokines and shear stress Enhance binding of its heterodimeric associated Tie-2 receptor to Ang-1	[107–110]	**γ-secretase**	[110]
Tie-2	Enhanced by PMA and VEGF	[262]		
TrkA	Enhanced by NGF	[263, 264]		
VEGFR-1	**ADAM10, ADAM17** Enhanced by PKC Regulated by the expression of VEGFR-2 and the presence of soluble VEGFR-1 ectodomain **BACE-1** Required for VEGF-induced angiogenesis in neural retina	[89]	**γ-secretase**	[90]
VEGFR-2	**ADAM17** Enhanced by VEGF-A	[265]		

Table 2

Functions of MRINs

RTK	Type	Functions	Ref
RON	holoreceptor	**Transcription regulator** Interacts with *c-JUN* promoter and HIF1α	[224]
EGFR	holoreceptor	**Transcription regulator** Interacts with RHA, MUC1, E2F1, STAT3/5 **DNA replication** Phosphorylates PCNA **DNA repair** Phosphorylates PCNA, ATM, histone H4 and interacts with DNA-PK	[17, 18, 25, 156, 158–165, 170–176]
EGFR	EGFRvIII	**Transcription regulator** Interacts with STAT3/5b	[164, 177]
EGFR	mLEEK	**Transcription regulator** Enhances transcription of GRP78	[32]
ErbB2	holoreceptor	**Transcription regulator** Interacts with STAT3, phosphorylate histone H2A1.2 **Anti-apoptosis** Phosphorylates Cdc2	[178, 182–185]
ErbB2	611-CTF	**Transcription regulator** Enhances metastasis-related genes, e.g., *MET, EPH2, MMP1, IL-11* and *Integrin* **Cell mobility** Phosphorylates cortactin	[187, 188]
ErbB3	holoreceptor	**Cell survival** Nuclear ErbB3 negatively correlates with cell survival and cancer recurrence	[191]
ErbB3	80-kDa	**Transcription regulator** Regulates cyclin-D1 promoter	[196]
ErbB3	50-kDa	**Transcription regulator** Regulates transcription activity and distribution of ezrin	[198]
ErbB4	4ICD	**Transcription regulator** Interacts with YAP, ERβ, STAT5A, N-CoR, TAB-2, HF1α Regulates *β*-casein expression	[147, 149–151, 199, 200]
FGFR1	holoreceptor	**Transcription regulator** Interacts with CREB-binding protein Phosphorylates RSK1	[145, 204, 205]
FGFR2	holoreceptor	**Transcription regulator** Interacts with STAT5 Correlates with poor prognosis in breast cancer	[206, 207]
VEGFR1	holoreceptor	**Cell survival**	[212]
VEGFR1	ICD	**Transcription regulator** [potential] Promotes angiogenesis	[211, 213, 214]
VEGFR2	holoreceptor	**Transcription regulator** Binds to transcriptional factor Sp1 **Wound healing**	[216, 217]
MET	holoreceptor	**Cell proliferation** Induces InsP3-dependent calcium release	[218]
MET	ICD	**Transcription regulator*** Interacts with YAP **Cell survival and reporgramming** Enhances SOX9 and β-catenin signals Upregulates NANOG protein level	[219–221]
ROR1		**Transcription regulator** Regulates actin cytoskeleton related gene transcription	[231, 232]
PDGFRα	holoreceptor	**Embryonic and lung development** [mouse model]	[235, 236]

RTK	Type	Functions	Ref
CSF1R	holoreceptor	**Transcription regulator** Enhances expression of CSF-1, CCND1, c-Myc and c-JUN	[237]
CSF1R	ICD	**Macrophage activation***	[81]
IGF1R		**Transcription regulator*** Binds to chromatin	[240]
InsR		**Transcription regulator** [Heterodimer of InsR/IGF1R] Promotes cell proliferation and anti-apoptosis Regulates cell cycle	[241]
Ryk	ICD	**Embryonic neuronal differentiation** [mouse model]	[117, 146]
PTK7	CTF2 (ICD)	**Cell proliferation and migration**	[120]
PTK7	CTF1 and 2 (ICD)	Phosphorylates CREB/ATF1	[249]
Mer		**Transcription regulator*** Binds to chromatin	[253]

*Predicted roles.